	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	334	beta$1catenin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:47			0
2	BRS	L2	10884	transcription adj factor	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:48			0
3	BRS	L3	869	(tumor adj suppressor adj gene adj product) or (tumor adj suppressor adj protein)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:50			0
4	BRS	L4	9122	lef-1 or tcf-4 or apc or conductin or e-cadherin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:50			0
5	BRS	L5	175	1 same (2 or 3 or 4)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:51			0
6	BRS	L6	62	5 same interact$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 13:52			0
7	BRS	L7	26	5 same interact$3 same (inhibit$3 or affect$3)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 14:06			0
8	BRS	L8	9	birchmeier adj walter.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 14:07			0
9	BRS	L9	2	von adj kries adj jens-peter.in.	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 14:07			0
10	BRS	L10	1	(8 or 9) and 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/02/18 14:08			0

=> d his

(FILE 'HOME' ENTERED AT 14:12:17 ON 18 FEB 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
14:12:44 ON 18 FEB 2003
L1 15203 S BETA CATENIN
L2 319392 S TRANSCRIPTION FACTOR
L3 12899 S (TUMOR SUPPRESSOR GENE PRODUCT) OR (TUMOR SUPPRESSOR PROTEIN)
L4 59642 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L5 386028 S L2 OR L3 OR L4
L6 1839 S L1 (P) L5 (P) INTERACT?
L7 535 S L6 (P) INHIBIT?
L8 180 S L6 (P) AFFECT?
L9 0 S L1 (P) (ARMADILLO ADJ DOMAIN)
L10 27 S (L7 OR L8) (P) PEPTIDE
L11 6 DUPLICATE REMOVE L10 (21 DUPLICATES REMOVED)
L12 1919 S L1 (P) (FRAGMENT OR MUTANT)
L13 334 S L12 (P) L5 (P) INTERACT?
L14 142 S L13 (P) (INHIBIT? OR AFFECT?)
L15 35 DUPLICATE REMOVE L14 (107 DUPLICATES REMOVED)
L16 32 S L15 NOT L11

=> log y

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FILE 'MEDLINE' ENTERED AT 14:12:44 18 FEB 2003

FILE 'CAPLUS' ENTERED AT 14:12:44 ON 18 FEB 2003
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FILE 'AGRICOLA' ENTERED AT 14:12:44 ON 18 FEB 2003

=> s beta catenin
L1       15203 BETA CATENIN

=> s transcription factor
L2      319392 TRANSCRIPTION FACTOR

=> s (tumor suppressor gene product) or (tumor suppressor protein)
   4 FILES SEARCHED...
L3       12899 (TUMOR SUPPRESSOR GENE PRODUCT) OR (TUMOR SUPPRESSOR PROTEIN)

=> s lef-1 or tcf-4 or apc or conductin or e-cadherin
L4       59642 LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN

=> s l2 or l3 or l4
L5      386028 L2 OR L3 OR L4

=> s l1 (p) l5 (p) interact?
L6        1839 L1 (P) L5 (P) INTERACT?

=> s l6 (p) inhibit?
L7         535 L6 (P) INHIBIT?

=> s l6 (p) affect?
L8         180 L6 (P) AFFECT?

=> s  l1 (p) (armadillo adj domain)
L9           0 L1 (P) (ARMADILLO ADJ DOMAIN)

=> s (l7 or l8) (p) Peptide
L10         27 (L7 OR L8) (P) PEPTIDE

=> duplicate remove l10
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L10
L11           6 DUPLICATE REMOVE L10 (21 DUPLICATES REMOVED)

=> d l11 1-6 ibib abs

L11  ANSWER 1 OF 6     MEDLINE                          DUPLICATE 1
ACCESSION NUMBER:   2002405105     MEDLINE
DOCUMENT NUMBER:    22072105   PubMed ID: 12077367
TITLE:              Regulation of S33/S37 phosphorylated beta-catenin in normal
                    and transformed cells.
AUTHOR:             Sadot Einat; Conacci-Sorrell Maralice; Zhurinsky Jacob;
                    Shnizer Dalia; Lando Zeev; Zharhary Dorit; Kam Zvi;
                    Ben-Ze'ev Avri; Geiger Benjamin
CORPORATE SOURCE:   Department of Molecular Cell Biology, Weizmann Institute of
                    Science Rehovot 76100 Israel.
SOURCE:             JOURNAL OF CELL SCIENCE, (2002 Jul 1) 115 (Pt 13) 2771-80.
                    Journal code: 0052457. ISSN: 0021-9533.
PUB. COUNTRY:       England: United Kingdom
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
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LANGUAGE: English
FILE SEGMENT: Priority Journ
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 20020806
Last Updated on STN: 20021214
Entered Medline: 20021126

AB A novel phosphorylation-specific antibody (alphapbeta-catenin) was generated against a ***peptide*** corresponding to amino acids 33-45 of human ***beta*** - ***catenin*** , which contained phosphorylated serines at positions 33 and 37. This antibody is specific to phosphorylated ***beta*** - ***catenin*** and reacts neither with the non-phosphorylated protein nor with phosphorylated or non-phosphorylated plakoglobin. It weakly ***interacts*** with S33Y ***beta*** - ***catenin*** but not with the S37A mutant. pbeta-catenin is hardly detectable in normal cultured cells and accumulates (up to 55% of total ***beta*** - ***catenin***) upon overexpression of the protein or after blocking its degradation by the proteasome. ***Inhibition*** of both GSK-3beta and the proteasome resulted in a rapid (t1/2=10 minutes) and reversible reduction in pbeta-catenin levels, suggesting that the protein can undergo dephosphorylation in live cells, at a rate comparable to its phosphorylation by GSK-3beta. pbeta-catenin ***interacts*** with ***LEF*** - ***1*** , but fails to form a ternary complex with DNA, suggesting that it is transcriptionally inactive. Immunofluorescence microscopy indicated that pbeta-catenin accumulates in the nuclei of MDCK and BCAP cells when overexpressed and is transiently associated with adherens junctions shortly after their formation. pbeta-catenin only weakly ***interacts*** with co-transfected N-cadherin, although it forms a complex with the ubiquitin ligase component beta-TrCP. SW480 colon cancer cells that express a truncated ***APC*** , at position 1338, contain high levels of pbeta-catenin, whereas HT29 cells, expressing ***APC*** truncated at position 1555, accumulate non-phosphorylated ***beta*** - ***catenin*** , suggesting that the 1338-1555 amino acid region of ***APC*** is involved in the differential regulation of the dephosphorylation and degradation of pbeta-catenin.

L11 ANSWER 2 OF 6 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2002221111 MEDLINE
DOCUMENT NUMBER: 21957086 PubMed ID: 11960376
TITLE: UCS15A, a novel small molecule, SH3 domain-mediated protein-protein interaction blocking drug.
AUTHOR: Oneyama Chitose; Nakano Hirofumi; Sharma Sreenath V
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co., Ltd 3-6-6 Asahi-cho, Machida-shi, Tokyo 194, Japan.
SOURCE: ONCOGENE, (2002 Mar 27) 21 (13) 2037-50.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200205
ENTRY DATE: Entered STN: 20020418
Last Updated on STN: 20020511
Entered Medline: 20020510

AB Protein-protein ***interactions*** play critical regulatory roles in mediating signal transduction. Previous studies have identified an unconventional, small-molecule, Src signal transduction ***inhibitor*** , UCS15A. UCS15A differed from conventional Src- ***inhibitors*** in that it did not alter the levels or the tyrosine kinase activity of Src. Our studies suggested that UCS15A exerted its Src- ***inhibitory*** effects by a novel mechanism that involved the disruption of protein-protein ***interactions*** mediated by Src. In the present study we have examined the ability of UCS15A to disrupt the ***interaction*** of Src-SH3 with Sam68, both in vivo and in vitro. This ability of UCS15A was not restricted to Src-SH3 mediated protein-protein ***interactions*** , since the drug was capable of disrupting the in vivo ***interactions*** of Sam68 with other SH3 domain containing proteins such as Grb2 and PLCgamma. In addition, UCS15A was capable of disrupting other typical SH3-mediated protein-protein ***interactions*** such as Grb2-Sos1, cortactin-ZO1, as well as atypical SH3-mediated protein-protein ***interactions*** such as Grb2-Gab1. However, UCS15A was unable to disrupt the non-SH3-mediated protein-protein ***interactions*** of

beta - ***catenin***, with ***E*** - ***cadherin*** and alpha-catenin. In addition, UCS15A had no effect on the SH2-mediated ***interaction*** between Grb2 and activated Epidermal Growth Factor receptor. Thus, the ability of UCS15A, to disrupt protein-protein ***interactions*** appeared to be restricted to SH3-mediated protein-protein ***interactions*** . In this regard, UCS15A represents the first example of a non- ***peptide*** , small molecule agent capable of disrupting SH3-mediated protein-protein ***interactions*** . In vitro analyses suggested that UCS15A did not bind to the SH3 domain itself but rather may ***interact*** directly with the target proline-rich domains.

L11 ANSWER 3 OF 6 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2002109278 MEDLINE
DOCUMENT NUMBER: 21819413 PubMed ID: 11818547
TITLE: Casein kinase I phosphorylates and destabilizes the beta-catenin degradation complex.
AUTHOR: Gao Zhong-Hua; Seeling Joni M; Hill Virginia; Yochum April; Virshup David M
CORPORATE SOURCE: Department of Oncological Sciences, Huntsman Cancer Institute, 2000 East North Campus Drive, University of Utah, Salt Lake City, UT 84112-5550, USA.
CONTRACT NUMBER: 2P30CA42014 (NCI)
R01CA71074 (NCI)
R01CA80809 (NCI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Feb 5) 99 (3) 1182-7. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020214
Last Updated on STN: 20030105
Entered Medline: 20020307
AB Wnt signaling plays a key role in cell proliferation and development. Recently, casein kinase I (CKI) and protein phosphatase 2A (PP2A) have emerged as positive and negative regulators of the Wnt pathway, respectively. However, it is not clear how these two enzymes with opposing functions regulate Wnt signaling. Here we show that both CKI delta and CKI epsilon ***interacted*** directly with Dvl-1, and that CKI phosphorylated multiple components of the Wnt-regulated ***beta*** - ***catenin*** degradation complex in vitro, including Dvl-1, adenomatous polyposis coli (***APC***), axin, and ***beta*** - ***catenin*** . Comparison of ***peptide*** maps from in vivo and in vitro phosphorylated ***beta*** - ***catenin*** and axin suggests that CKI phosphorylates these proteins in vivo as well. CKI abrogated ***beta*** - ***catenin*** degradation in Xenopus egg extracts. Notably, CKI decreased, whereas ***inhibition*** of CKI increased, the association of PP2A with the ***beta*** - ***catenin*** degradation complex in vitro. Additionally, ***inhibition*** of CKI in vivo stabilized the ***beta*** - ***catenin*** degradation complex, suggesting that CKI actively destabilizes the complex in vivo. The ability of CKI to induce secondary body axes in Xenopus embryos was reduced by the B56 regulatory subunit of PP2A, and kinase-dead CKI epsilon acted synergistically with B56 in ***inhibiting*** Wnt signaling. The data suggest that CKI phosphorylates and destabilizes the ***beta*** - ***catenin*** degradation complex, likely through the dissociation of PP2A, providing a mechanism by which CKI stabilizes ***beta*** - ***catenin*** and propagates the Wnt signal.

L11 ANSWER 4 OF 6 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1999452924 MEDLINE
DOCUMENT NUMBER: 99452924 PubMed ID: 10521419
TITLE: Suppression of glycogen synthase kinase activity is not sufficient for leukemia enhancer factor-1 activation.
AUTHOR: Yuan H; Mao J; Li L; Wu D
CORPORATE SOURCE: Department of Pharmacology, University of Rochester, New York 14642, USA.
CONTRACT NUMBER: GM53162 (NIGMS)
GM54167 (NIGMS)

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1999 Oct 22) 274 (43) 30419-23.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20021218
Entered Medline: 19991123

AB Glycogen synthase kinase-3 (GSK) can be regulated by different signaling pathways including those mediated by protein kinase Akt and Wnt proteins. Wnt proteins are believed to activate a ***transcription*** ***factor*** leukemia enhancer factor-1 (***LEF*** - ***1***) by ***inhibiting*** GSK, and Akt was shown to phosphorylate GSK and ***inhibit*** its kinase activity. We investigated the effect of an activated Akt on the accumulation of cytosolic ***beta*** - ***catenin*** and ***LEF*** - ***1*** -dependent transcription. Although the activated Akt, mAkt, clearly ***inhibited*** the kinase activity of GSK, mAkt alone did not induce accumulation of cytosolic ***beta*** - ***catenin*** or activate ***LEF*** - ***1*** -dependent transcription. On the contrary, coexpressed Wnt-1 and Frat activated ***LEF*** - ***1*** but did not show significant ***inhibition*** of GSK-mediated phosphorylation of a ***peptide*** substrate. However, mAkt could act synergistically with Wnt-1 or Frat to activate ***LEF*** - ***1*** . In addition, the ***interaction*** of GSK for Axin appeared to decrease in the presence of mAkt, whereas the ***interaction*** for Frat remained unchanged. Consistently, a GSK mutant with substitution of a Phe residue for residue Tyr-216, which showed one-fifth of kinase activity of the wild-type GSK, exhibited a reduced association for Axin than the wild-type GSK. These results suggest that ***inhibition*** of GSK kinase activity is not sufficient for activation of ***LEF*** - ***1*** but may facilitate the activation by reducing the ***interaction*** of GSK for Axin. The additional mechanism for ***LEF*** - ***1*** activation may require dissociation of GSK from Axin as Frat facilitates the dissociation of GSK from Axin.

L11 ANSWER 5 OF 6 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1998440064 MEDLINE
DOCUMENT NUMBER: 98440064 PubMed ID: 9769128
TITLE: TPA-induced cohort migration of well-differentiated human rectal adenocarcinoma cells: cells move in a RGD-dependent manner on fibronectin produced by cells, and phosphorylation of E-cadherin/catenin complex is induced independently of cell-extracellular matrix interactions.
AUTHOR: Nabeshima K; Inoue T; Shimao Y; Kataoka H; Koono M
CORPORATE SOURCE: Department of Pathology, Miyazaki Medical College, Kiyotake, Japan.
SOURCE: VIRCHOWS ARCHIV, (1998 Sep) 433 (3) 243-53.
Journal code: 9423843. ISSN: 0945-6317.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199810
ENTRY DATE: Entered STN: 19981029
Last Updated on STN: 19981029
Entered Medline: 19981022

AB We have already presented a two-dimensional cell motility assay using a highly metastatic variant (L-10) of human rectal adenocarcinoma cell line RCM-1 as a motility model of tumour cells of epithelial origin. In this model, L-10 cells showed locomotion as a coherent sheet when stimulated with 12-O-tetradecanoylphorbol-13-acetate (TPA), and we called this type of movement "cohort migration". Electron and immunoelectron microscopic study of the migrating cell sheets demonstrated localized release from cell-cell adhesion only at the lower portion of the cells with loss of ***E*** - ***cadherin*** immunoreactivity, and this change was associated with increased tyrosine phosphorylation of the ***E*** - ***cadherin*** -catenin complex, including ***beta*** - ***catenin*** . Cell-extracellular matrix (ECM) ***interactions*** involved in this

TPA-induced cohort migration and their effect on tyrosine phosphorylation of the ***E*** - ***cadhe***** -catenin complex have now been investigated. L-10 cell cohort migration was almost completely ***inhibited*** by addition of Arg-Gly-Asp (RGD) ***peptide*** into the medium, and thus RGD dependent. Cohort migration was stimulated on type I and IV collagens, fibronectin (FN)- and laminin-coated substratum, but was ***inhibited*** by RGD only on FN-coated surface. By using immunofluorescent techniques, FN was demonstrated preferentially around migrating cells, and a protein synthesis ***inhibitor*** , cycloheximide, ***inhibited*** the migration by about 75%. FN produced by L-10 cells were found to be mostly EDA+ FN when analysed by RT-PCR. Moreover, anti-FN antibody, but not anti-vitronectin antibody, ***inhibited*** the TPA-induced cohort migration almost completely. Thus, it was likely that L-10 cells produced FN themselves and moved on the FN substrate in an RGD-dependent manner. However, stimulation of migration by type I collagen coating and ***inhibition*** by RGD treatment did not ***affect*** the tyrosine phosphorylation of the ***E*** - ***cadherin*** -catenin complex induced by TPA, indicating that cell-cell ***interactions*** were adjusted to suit cell migration, irrespective of the condition of cell-ECM adhesion, during TPA-induced cohort migration.

L11 ANSWER 6 OF 6 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998162711 MEDLINE
DOCUMENT NUMBER: 98162711 PubMed ID: 9501980
TITLE: Nuclear localization signal-independent and importin/karyopherin-independent nuclear import of beta-catenin.
AUTHOR: Fagotto F; Gluck U; Gumbiner B M
CORPORATE SOURCE: Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York 10021, USA.
CONTRACT NUMBER: GM37432 (NIGMS)
P30-CA-08748 (NCI)
SOURCE: CURRENT BIOLOGY, (1998 Feb 12) 8 (4) 181-90.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 19980520
Last Updated on STN: 19980520
Entered Medline: 19980513

AB BACKGROUND: Control of the nuclear localization of specific proteins is an important mechanism for regulating many signal transduction pathways. Upon activation of the Wnt signaling pathway, ***beta*** - ***catenin*** localizes into the nucleus and ***interacts*** with TCF/ ***LEF*** - ***1*** (T-cell factor/lymphocyte enhancer factor-1) ***transcription*** ***factors*** , triggering activation of downstream genes. The role of regulated nuclear localization in ***beta*** - ***catenin*** signaling is still unclear. ***Beta*** - ***catenin*** has no nuclear localization sequence (NLS). Although it has been reported that ***beta*** - ***catenin*** can piggyback into the nucleus by binding to TCF/ ***LEF*** - ***1*** , there is evidence that its import is independent of TCF/ ***LEF*** - ***1*** in vivo. Therefore, the mechanism for ***beta*** - ***catenin*** nuclear localization remains to be established. RESULTS: We have analyzed ***beta*** - ***catenin*** nuclear import in an in vitro assay using permeabilized cells. ***Beta*** - ***catenin*** docks specifically onto the nuclear envelope in the absence of other cytosolic factors. Docking is not ***inhibited*** by an NLS ***peptide*** and does not require importins/karyopherins, the receptors for classical NLS substrates. Rather, docking is specifically competed by importin-beta/beta-karyopherin, indicating that ***beta*** - ***catenin*** and importin-beta/beta-karyopherin both ***interact*** with common nuclear pore components. Nuclear translocation of ***beta*** - ***catenin*** is energy dependent and is ***inhibited*** by nonhydrolyzable GTP analogs and by a dominant-negative mutant form of the Ran GTPase. Cytosol preparations contain ***inhibitory*** activities for ***beta*** - ***catenin*** import that are distinct from the competition by importin-beta/beta-karyopherin and may be involved in the physiological regulation of the pathway. CONCLUSIONS: ***Beta*** -

catenin is imported into the nucleus by binding directly to the nuclear pore machinery, simil[redacted]to importin-beta/beta-karyophe[redacted] or other importin-beta-like import factors, such as transportin. These findings provide an explanation for how ***beta*** - ***catenin*** localizes to the nucleus without an NLS and independently of its ***interaction*** with TCF/ ***LEF*** - ***1*** . This is a new and unusual mechanism for the nuclear import of a signal transduction protein. The lack of ***beta*** - ***catenin*** import activity in the presence of normal cytosol suggests that its import may be regulated by upstream events in the Wnt signaling pathway.

=> d his

(FILE 'HOME' ENTERED AT 14:12:17 ON 18 FEB 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT 14:12:44 ON 18 FEB 2003

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L1         15203 S BETA CATENIN
L2        319392 S TRANSCRIPTION FACTOR
L3         12899 S (TUMOR SUPPRESSOR GENE PRODUCT) OR (TUMOR SUPPRESSOR PROTEIN)
L4         59642 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L5        386028 S L2 OR L3 OR L4
L6          1839 S L1 (P) L5 (P) INTERACT?
L7           535 S L6 (P) INHIBIT?
L8           180 S L6 (P) AFFECT?
L9             0 S  L1 (P) (ARMADILLO ADJ DOMAIN)
L10           27 S (L7 OR L8) (P) PEPTIDE
L11            6 DUPLICATE REMOVE L10 (21 DUPLICATES REMOVED)

=> s l1 (p) (fragment or mutant)
L12        1919 L1 (P) (FRAGMENT OR MUTANT)

=> s l12 (p) l5 (p) interact?
L13         334 L12 (P) L5 (P) INTERACT?

=> s l13 (p) (inhibit? or affect?)
L14         142 L13 (P) (INHIBIT? OR AFFECT?)

=> duplicate remove l14
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L14
L15           35 DUPLICATE REMOVE L14 (107 DUPLICATES REMOVED)

=> s l15 not l11
L16          32 L15 NOT L11

=> d l16 1-32 ibib abs

L16  ANSWER 1 OF 32     MEDLINE
ACCESSION NUMBER:   2003047483     IN-PROCESS
DOCUMENT NUMBER:    22444688   PubMed ID: 12556497
TITLE:              Regulation of Lymphoid Enhancer Factor 1/T-Cell Factor by
                    Mitogen-Activated Protein Kinase-Related Nemo-Like
                    Kinase-Dependent Phosphorylation in Wnt/beta-Catenin
                    Signaling.
AUTHOR:             Ishitani Tohru; Ninomiya-Tsuji Jun; Matsumoto Kunihiro
CORPORATE SOURCE:   Department of Molecular Biology, Graduate School of
                    Science, Nagoya University, and CREST, Japan Science and
                    Technology Corporation, Chikusa-ku, Nagoya 464-8602, Japan.
SOURCE:             MOLECULAR AND CELLULAR BIOLOGY, (2003 Feb) 23 (4) 1379-89.
                    Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY:       United States
DOCUMENT TYPE:      Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:           English
FILE SEGMENT:       IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE:         Entered STN: 20030131
                    Last Updated on STN: 20030131
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AB The Wnt/ ***beta*** - ***catenin*** signaling pathway regulates many developmental processes by modulating gene expression. Wnt signaling induces the stabilization of cytosolic ***beta*** - ***catenin*** ,

which then associates with lymphoid enhancer factor and T-cell factor (***LEF*** - ***1*** /TCF) to form a transcription complex that activates Wnt target genes. Previously, we have shown that a specific mitogen-activated protein (MAP) kinase pathway involving the MAP kinase kinase kinase TAK1 and MAP kinase-related Nemo-like kinase (NLK) suppresses Wnt signaling. In this study, we investigated the relationships among NLK, ***beta*** - ***catenin*** , and ***LEF*** - ***1*** /TCF. We found that NLK ***interacts*** directly with ***LEF*** - ***1*** /TCF and indirectly with ***beta*** - ***catenin*** via ***LEF*** - ***1*** /TCF to form a complex. NLK phosphorylates ***LEF*** - ***1*** /TCF on two serine/threonine residues located in its central region. Mutation of both residues to alanine enhanced ***LEF*** - ***1*** transcriptional activity and rendered it resistant to ***inhibition*** by NLK. Phosphorylation of ***TCF*** - ***4*** by NLK ***inhibited*** DNA binding by the ***beta*** - ***catenin*** - ***TCF*** - ***4*** complex. However, this ***inhibition*** was abrogated when a ***mutant*** form of ***TCF*** - ***4*** was used in which both threonines were replaced with valines. These results suggest that NLK phosphorylation on these sites contributes to the down-regulation of ***LEF*** - ***1*** /TCF transcriptional activity.

L16 ANSWER 2 OF 32 MEDLINE
ACCESSION NUMBER: 2002704423 MEDLINE
DOCUMENT NUMBER: 22354739 PubMed ID: 12466965
TITLE: Ligand-dependent inhibition of beta-catenin/TCF signaling by androgen receptor. T cell factor.
AUTHOR: Chesire Dennis R; Isaacs William B
CORPORATE SOURCE: Brady Urological Institute Research Laboratories, The Johns Hopkins Medical Institutions, Baltimore, Maryland, MD 21287, USA.
CONTRACT NUMBER: CA58236 (NCI)
SOURCE: ONCOGENE, (2002 Dec 5) 21 (55) 8453-69.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 20021217
Last Updated on STN: 20030107
Entered Medline: 20030106

AB ***Beta*** - ***catenin*** signaling may contribute to prostate cancer (CaP) progression. Although ***beta*** - ***catenin*** is known to upregulate T cell factor (TCF) target gene expression in CaP cells, recent evidence demonstrates its capacity to enhance ligand-dependent androgen receptor (AR) function. Thus, we wished to further understand the ***interaction*** between these two pathways. We find in both CaP cells (CWR22-Rv1, LAPC-4, DU145) and non-CaP cells (HEK-293, TSU, SW480, HCT-116) that ***beta*** - ***catenin*** /TCF-related transcription (CRT), as measured by activation of a synthetic promoter and that of cyclin D1, is ***inhibited*** by androgen treatment. This ***inhibition*** is AR-dependent, as it only occurs in cells expressing AR endogenously or transiently, and is abrogated by AR antagonists. Additional analyses convey that the ligand-dependent nature of CRT suppression depends on transactivation-competent AR in the nucleus, but not on indirect effects stemming from AR target gene expression. Given the recent work identifying an AR/ ***beta*** - ***catenin*** ***interaction*** , and from our finding that liganded AR does not prompt gross changes in the constitutive nuclear localization of TCF4 or ***mutant*** ***beta*** - ***catenin*** , we hypothesized that ***transcription*** ***factor*** (i.e. AR and TCF) competition for ***beta*** - ***catenin*** recruitment may explain, in part, androgen-induced suppression of CRT. To address this idea, we expressed an AR ***mutant*** lacking its DNA-binding domain (DBD). This receptor could not orchestrate ligand-dependent CRT repression, thereby providing support for those recent data implicating the AR DBD/LBD as necessary for ***beta*** - ***catenin*** ***interaction*** . Further supporting this hypothesis, TCF/LEF over-expression counteracts androgen-induced suppression of CRT, and requires ***beta*** - ***catenin*** binding activity to do so. Interestingly, TCF4 over-expression potently antagonizes AR function; however, this ***inhibition*** may occur

independently of ***beta*** ***catenin*** /TCF4 ***interaction***. These results from TCF4 overexpression analyses, taken together, provide further evidence that AR-mediated suppression of CRT is a consequence of limiting amounts of ***beta*** - ***catenin*** , and not AR target gene expression. Our analyses point to a reciprocal balance between AR and CRT function that may shape critical processes during normal prostate development and tumor progression.

L16 ANSWER 3 OF 32 MEDLINE
ACCESSION NUMBER: 2002613671 MEDLINE
DOCUMENT NUMBER: 22258021 PubMed ID: 12370829
TITLE: The transmembrane receptor protein tyrosine phosphatase DEP1 interacts with p120(ctn).
AUTHOR: Holsinger Leslie J; Ward Kevin; Duffield Bill; Zachwieja Joseph; Jallal Bahija
CORPORATE SOURCE: SUGEN Inc., 230 East Grand Avenue, South San Francisco, California, CA 94080, USA.. leslie-holsinger@sugen.com
SOURCE: ONCOGENE, (2002 Oct 10) 21 (46) 7067-76.
Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200210
ENTRY DATE: Entered STN: 20021010
Last Updated on STN: 20021026
Entered Medline: 20021024

AB The receptor-like protein tyrosine phosphatase DEP1, also known as CD148, is expressed predominantly in epithelial cells, in a variety of tumor cell lines, and in lymphocytes. Expression of DEP1 is enhanced at high cell density, and this observation suggests that DEP1 may function in the regulation of cell adhesion and possibly contact ***inhibition*** of cell growth. In order to investigate the function of DEP1, substrate-trapping ***mutants*** of the phosphatase were used to identify potential substrates. GST-fusion proteins containing the DEP1 catalytic domain with a substrate-trapping D/A mutation were found to ***interact*** with p120(ctn), a component of adherens junctions. DEP1 also ***interacted*** with other members of the catenin gene family including ***beta*** - ***catenin*** and gamma-catenin. The ***interaction*** with p120(ctn) is likely to be direct, as the ***interaction*** occurs in K562 cells lacking functional adherens junctions and ***E*** - ***cadherin*** expression. Catalytic domains of the tyrosine phosphatases PTP-PEST, CD45, and PTPbeta did not ***interact*** with proteins of the catenin family to detectable levels, suggesting that the ***interaction*** of DEP1 with these proteins is specific. DEP1 expression was concentrated at sites of cell-cell contact in A549 cells. p120(ctn) was found to colocalize with these structures. Together these data suggest an important role for DEP-1 in the function of cell-cell contacts and adherens junctions.

L16 ANSWER 4 OF 32 MEDLINE
ACCESSION NUMBER: 2002421114 MEDLINE
DOCUMENT NUMBER: 22165307 PubMed ID: 12176738
TITLE: Regulation of endothelial barrier function and growth by VE-cadherin, plakoglobin, and beta-catenin.
AUTHOR: Venkiteswaran Kala; Xiao Kanyan; Summers Susan; Calkins Catharine C; Vincent Peter A; Pumiglia Kevin; Kowalczyk Andrew P
CORPORATE SOURCE: Department of Dermatology, Emory University School of Medicine, Atlanta, Georgia 30322, USA.
CONTRACT NUMBER: K01-AR-02039 (NIAMS)
P30-AR-042687 (NIAMS)
R01-CA-81419 (NCI)
R29-HL-054206 (NHLBI)
RPG-00-246-01 (OAPP)
T32-AR-007587 (NIAMS)
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. CELL PHYSIOLOGY, (2002 Sep) 283 (3) C811-21.
Journal code: 100901225. ISSN: 0363-6143.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200209
ENTRY DATE: Entered STN: 20020815
Last Updated on STN: 20020910
Entered Medline: 20020909

AB VE-cadherin is an endothelial-specific cadherin that plays a central role in vascular barrier function and angiogenesis. The cytoplasmic domain of VE-cadherin is linked to the cytoskeleton through ***interactions*** with the armadillo family proteins ***beta*** - ***catenin*** and plakoglobin. Growing evidence indicates that ***beta*** - ***catenin*** and plakoglobin play important roles in epithelial growth and morphogenesis. To test the role of these proteins in vascular cells, a replication-deficient retroviral system was used to express intercellular junction proteins and ***mutants*** in the human dermal microvascular endothelial cell line (HMEC-1). A ***mutant*** VE-cadherin lacking an adhesive extracellular domain disrupted endothelial barrier function and ***inhibited*** endothelial growth. In contrast, expression of exogenous plakoglobin or metabolically stable ***mutants*** of ***beta*** - ***catenin*** stimulated HMEC-1 cell growth, which suggests that the ***beta*** - ***catenin*** signaling pathway was active in HMEC-1 cells. This possibility was supported by the finding that a dominant-negative ***mutant*** of the ***transcription*** ***factor*** ***TCF*** - ***4*** , designed to ***inhibit*** ***beta*** - ***catenin*** signaling, also ***inhibited*** HMEC-1 cell growth. These observations suggest that intercellular junction proteins function as components of an adhesion and signaling system that regulates vascular barrier function and growth.

L16 ANSWER 5 OF 32 MEDLINE
ACCESSION NUMBER: 2002348432 MEDLINE
DOCUMENT NUMBER: 22086174 PubMed ID: 11976333
TITLE: Galpha12 and Galpha13 negatively regulate the adhesive functions of cadherin.
AUTHOR: Meigs Thomas E; Fedor-Chaiken Mary; Kaplan Daniel D; Brackenbury Robert; Casey Patrick J
CORPORATE SOURCE: Department of Pharmacology and Cancer Biology, Duke University Medical Center, Durham, North Carolina 27710, USA.
CONTRACT NUMBER: AR44713 (NIAMS)
CA91159 (NCI)
GM55717 (NIGMS)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jul 5) 277 (27) 24594-600.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 20020702
Last Updated on STN: 20030105
Entered Medline: 20020827

AB Cadherins function to promote adhesion between adjacent cells and play critical roles in such cellular processes as development, tissue maintenance, and tumor suppression. We previously demonstrated that heterotrimeric G proteins of the G12 subfamily comprised of Galpha12 and Galpha13 ***interact*** with the cytoplasmic domain of cadherins and cause the release of the transcriptional activator ***beta*** - ***catenin*** (Meigs, T. E., Fields, T. A., McKee, D. D., and Casey, P. J. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 519-524). Because of the importance of ***beta*** - ***catenin*** in cadherin-mediated cell-cell adhesion, we examined whether G12 subfamily proteins could also regulate cadherin function. The introduction of mutationally activated G12 proteins into K562 cells expressing ***E*** - ***cadherin*** blocked cadherin-mediated cell adhesion in steady-state assays. Also, in breast cancer cells, the introduction of activated G12 proteins blocked ***E*** - ***cadherin*** function in a fast aggregation assay. Aggregation mediated by a ***mutant*** cadherin that lacks G12 binding ability was not ***affected*** by activated G12 proteins, indicating a requirement for direct G12-cadherin ***interaction*** . Furthermore, in wound-filling assays in which ectopic expression of ***E*** - ***cadherin*** ***inhibits*** cell migration, the expression of

activated G12 proteins reversed the ***inhibition*** via a mechanism that was independent of G12-mediated Rho activation. These results validate the G12-cadherin ***interaction*** as a potentially important event in cell biology and suggest novel roles for G12 proteins in the regulation of cadherin-mediated developmental events and in the loss of cadherin function that is characteristic of metastatic tumor progression.

L16 ANSWER 6 OF 32 MEDLINE
ACCESSION NUMBER: 2002087037 MEDLINE
DOCUMENT NUMBER: 21668991 PubMed ID: 11809809
TITLE: Negative feedback loop of Wnt signaling through upregulation of conductin/axin2 in colorectal and liver tumors.
AUTHOR: Lustig Barbara; Jerchow Boris; Sachs Martin; Weiler Sigrid; Pietsch Torsten; Karsten Uwe; van de Wetering Marc; Clevers Hans; Schlag Peter M; Birchmeier Walter; Behrens Jurgen
CORPORATE SOURCE: Max Delbrueck Center for Molecular Medicine, D-13092 Berlin, Germany.
SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (2002 Feb) 22 (4) 1184-93. Journal code: 8109087. ISSN: 0270-7306.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020130
Last Updated on STN: 20020302
Entered Medline: 20020301
AB Activation of Wnt signaling through ***beta*** - ***catenin*** /TCF complexes is a key event in the development of various tumors, in particular colorectal and liver tumors. Wnt signaling is controlled by the negative regulator ***conductin*** /axin2/axil, which induces degradation of ***beta*** - ***catenin*** by functional ***interaction*** with the tumor suppressor ***APC*** and the serine/threonine kinase GSK3beta. Here we show that ***conductin*** is upregulated in human tumors that are induced by ***beta*** - ***catenin*** /Wnt signaling, i.e., high levels of ***conductin*** protein and mRNA were found in colorectal and liver tumors but not in the corresponding normal tissues. In various other tumor types, ***conductin*** levels did not differ between tumor and normal tissue. Upregulation of ***conductin*** was also observed in the ***APC*** -deficient intestinal tumors of Min mice. ***Inhibition*** of Wnt signaling by a dominant-negative ***mutant*** of TCF downregulated ***conductin*** but not the related protein, axin, in DLD1 colorectal tumor cells. Conversely, activation of Wnt signaling by Wnt-1 or dishevelled increased ***conductin*** levels in MDA MB 231 and Neuro2A cells, respectively. In time course experiments, stabilization of ***beta*** - ***catenin*** preceded the upregulation of ***conductin*** by Wnt-1. These results demonstrate that ***conductin*** is a target of the Wnt signaling pathway. Upregulation of ***conductin*** may constitute a negative feedback loop that controls Wnt signaling activity.

L16 ANSWER 7 OF 32 MEDLINE
ACCESSION NUMBER: 2002077369 MEDLINE
DOCUMENT NUMBER: 21648750 PubMed ID: 11711551
TITLE: The transcriptional factor Tcf-4 contains different binding sites for beta-catenin and plakoglobin.
AUTHOR: Miravet Susana; Piedra Jose; Miro Francesc; Itarte Emilio; Garcia de Herreros Antonio; Dunach Mireia
CORPORATE SOURCE: Unitat de Biofisica, Departament de Bioquimica i Biologia Molecular, Facultat de Medicina, Universitat Autonoma de Barcelona, 08193 Bellaterra, Spain.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Jan 18) 277 (3) 1884-91. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200202
ENTRY DATE: Entered STN: 20020128

Last Updated on STN: 20030105
Entered Medline: 20020213

AB ***beta*** - ***Catenin*** and plakoglobin are two related armadillo proteins necessary for the establishment of adhesion junctions and desmosomes. Moreover, ***beta*** - ***catenin*** can also act as a transcriptional co-activator through its ***interaction*** with the members of Tcf/ ***LEF*** - ***1*** transcriptional factor family. We show here that ***Tcf*** - ***4*** can be phosphorylated in vitro by protein kinase CK2 stoichiometrically in amino acids Ser-58-Ser-59-Ser-60. Phosphorylation of these residues does not modify the ***interaction*** of ***Tcf*** - ***4*** with ***beta*** - ***catenin*** but reduces its association to plakoglobin. The binding sites of ***Tcf*** - ***4*** for these two proteins were compared; whereas ***beta*** - ***catenin*** requires the N-terminal first 50 amino acids, plakoglobin ***interacts*** mainly with residues 51-80. ***Tcf*** - ***4*** -(51-80) binds plakoglobin in the region of armadillo repeats 1-6. Ternary complexes composed by ***beta*** - ***catenin*** / ***Tcf*** - ***4*** /plakoglobin could be detected in vitro, demonstrating that simultaneous binding of the two armadillo proteins to ***Tcf*** - ***4*** is possible. Experiments performed using a ***Tcf*** - ***4*** ***mutant*** with decreased ***interaction*** to plakoglobin demonstrated that binding to this protein negatively ***affected*** the transcriptional activity of ***Tcf*** - ***4*** . These results indicate that ***Tcf*** - ***4*** contains two different sites for binding of ***beta*** - ***catenin*** and plakoglobin, and the ***interaction*** of the latter hinders the transcriptional activity of the complex.

L16 ANSWER 8 OF 32 MEDLINE
ACCESSION NUMBER: 2002003046 MEDLINE
DOCUMENT NUMBER: 21623063 PubMed ID: 11751639
TITLE: Chromatin-specific regulation of LEF-1-beta-catenin transcription activation and inhibition in vitro.
AUTHOR: Tutter A V; Fryer C J; Jones K A
CORPORATE SOURCE: Regulatory Biology Laboratory, The Salk Institute for Biological Studies, La Jolla, California 92037, USA.
SOURCE: GENES AND DEVELOPMENT, (2001 Dec 15) 15 (24) 3342-54. Journal code: 8711660. ISSN: 0890-9369.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20020102
Last Updated on STN: 20020125
Entered Medline: 20020122

AB Transcriptional activation of Wnt/Wg-responsive genes requires the stabilization and nuclear accumulation of ***beta*** - ***catenin*** , a dedicated coactivator of LEF/TCF enhancer-binding proteins. Here we report that recombinant ***beta*** - ***catenin*** strongly enhances binding and transactivation by ***LEF*** - ***1*** on chromatin templates in vitro. Interestingly, different ***LEF*** - ***1*** isoforms vary in their ability to bind nucleosomal templates in the absence of ***beta*** - ***catenin*** , owing to N-terminal residues that repress binding to chromatin, but not nonchromatin, templates. Transcriptional activation in vitro requires both the armadillo (ARM) repeats and the C terminus of ***beta*** - ***catenin*** , whereas the phosphorylated N terminus is ***inhibitory*** to transcription. A ***fragment*** spanning the C terminus (CT) and ARM repeats 11 and 12 (CT-ARM), but not the CT alone, functions as a dominant negative ***inhibitor*** of ***LEF*** - ***1*** -beta-cat activity in vitro and can block ATP-dependent binding of the complex to chromatin. ***LEF*** - ***1*** -beta-cat transactivation in vitro was also repressed by ***inhibitor*** of ***beta*** - ***catenin*** and ***Tcf*** - ***4*** (ICAT), a physiological ***inhibitor*** of Wnt/Wg signaling that ***interacts*** with ARM repeats 11 and 12, and by the nonsteroidal anti-inflammatory compound, sulindac. None of these transcription ***inhibitors*** (CT-ARM, ICAT, or sulindac) could disrupt the ***LEF*** - ***1*** -beta-cat complex after it was stably bound to chromatin. We conclude that the CT-ARM region of ***beta*** - ***catenin*** functions as a chromatin-specific activation domain, and that several ***inhibitors*** of the Wnt/Wg pathway directly modulate

LEF - ***1*** -beta-cat activity on chromatin.

L16 ANSWER 9 OF 32 MEDLINE
ACCESSION NUMBER: 2001665781 MEDLINE
DOCUMENT NUMBER: 21568063 PubMed ID: 11712088
TITLE: Expression and interaction of different catenins in colorectal carcinoma cells.
AUTHOR: Kucerova D; Sloncova E; Tuhackova Z; Vojtechova M; Sovova V
CORPORATE SOURCE: Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, 166 37 Praha 6, Czech Republic.
SOURCE: INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, (2001 Dec) 8 (6) 695-8.
Journal code: 9810955. ISSN: 1107-3756.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20011119
Last Updated on STN: 20020307
Entered Medline: 20020306
AB Aberrant signalling activities of ***beta*** - ***catenin*** , originally identified as a component of cell-adhesion complexes, are now considered to be an important factor in colorectal carcinogenesis. However, recently it was shown that also gamma- as well as p120 catenins have a dual role either in cell adhesion or in ***affecting*** some gene activation. Therefore, the levels and ***interactions*** of these three catenins in human colorectal carcinoma cell lines were analysed. A great heterogeneity in the expression of all catenins tested was found in colorectal carcinoma cell lines HT29 and LS174T. Detailed analysis of ***beta*** - ***catenin*** ***interactions*** was done. GST-***APC*** ***fragment*** -fused proteins were used to absorb ***beta*** - ***catenin*** and its complexes from cell lysates. Similarly, the ***E*** - ***cadherin*** binding capacity of the residual pool of ***beta*** - ***catenin*** was analysed using the GST-ECT construct. It was found that the level of ***beta*** - ***catenin*** does not necessarily depend either on the ***APC*** or ***beta*** - ***catenin*** gene mutations and that co-precipitation of beta-, gamma-, and p120 catenins is not limited to cells that express ***E*** - ***cadherin*** .

L16 ANSWER 10 OF 32 MEDLINE
ACCESSION NUMBER: 2001567875 MEDLINE
DOCUMENT NUMBER: 21486490 PubMed ID: 11504726
TITLE: Presenilin 1 regulates beta-catenin-mediated transcription in a glycogen synthase kinase-3-independent fashion.
AUTHOR: Palacino J J; Murphy M P; Murayama O; Iwasaki K; Fujiwara M; Takashima A; Golde T E; Wolozin B
CORPORATE SOURCE: Department of Pharmacology and Neuroscience Program, Loyola University Medical Center, Maywood, Illinois 60153, USA.
CONTRACT NUMBER: 1F31MH12479 (NIMH)
AG17485 (NIA)
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2001 Oct 19) 276 (42) 38563-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011025
Last Updated on STN: 20030105
Entered Medline: 20011204
AB Presenilin 1 (PS1) is linked with Alzheimer's disease but exhibits functional roles regulating growth and development. For instance, PS1 binds to ***beta*** - ***catenin*** and modulates ***beta*** - ***catenin*** signaling. In the current study, we observed that knockout of PS1 ***inhibited*** ***beta*** - ***catenin*** -mediated transcription by 35%, as shown by a luciferase reporter driven by the hTcf-4 promoter. Overexpressing wild-type PS1 increased ***beta*** - ***catenin*** -mediated transcription by 37.5%, and overexpressing PS1 with mutations associated with Alzheimer's disease decreased ***beta***

- ***catenin*** -mediated transcription by 66%. To examine whether regulation of ***beta*** - ***catenin*** by PS1 requires phosphorylation by glycogen synthase kinase 3beta (GSK 3beta), we examined whether ***inhibiting*** GSK 3beta activity overcomes the ***inhibition*** of ***beta*** - ***catenin*** transcription induced by ***mutant*** PS1 constructs. Cells expressing wild-type or ***mutant*** PS1 were treated with LiCl, which ***inhibits*** GSK 3beta, or transfected with ***beta*** - ***catenin*** constructs that lack the GSK 3beta phosphorylation sites. Neither treatment overcame PS1-mediated ***inhibition*** of ***beta*** - ***catenin*** signaling, suggesting that regulation of ***beta*** - ***catenin*** by PS1 was not ***affected*** by the activity of GSK 3beta. To investigate how PS1 might regulate ***beta*** - ***catenin*** signaling, we determined whether PS1 ***interacts*** with other elements of the ***beta*** - ***catenin*** signaling cascade, such as the ***Tcf*** - ***4*** ***transcription*** ***factor*** . Coimmunoprecipitation studies showed binding of PS1 and hTcf-4, and examining nuclear isolates indicated that nuclear hTcf-4 was decreased in cells expressing ***mutant*** PS1. These data show that PS1 ***interacts*** with multiple components of the ***beta*** - ***catenin*** signaling cascade and suggest that PS1 regulates ***beta*** - ***catenin*** in a manner independent of GSK 3beta activity.

L16 ANSWER 11 OF 32 MEDLINE
ACCESSION NUMBER: 2001460949 MEDLINE
DOCUMENT NUMBER: 21382257 PubMed ID: 11489917
TITLE: Expression of alpha-catenin in alpha-catenin-deficient cells increases resistance to sphingosine-induced apoptosis.
AUTHOR: Matsubara S; Ozawa M
CORPORATE SOURCE: Department of Biochemistry, Faculty of Medicine, Kagoshima University, Kagoshima 890-8520, Japan.. shmlmcbd@m.kufm.kagoshima-u.ac.jp
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Aug 6) 154 (3) 573-84. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200109
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010910
Entered Medline: 20010906

AB Alpha-catenin, an intracellular protein, associates with the COOH-terminal region of cadherin cell adhesion molecules through ***interactions*** with either ***beta*** - ***catenin*** or gamma-catenin (plakoglobin). The full activity of cadherins requires a linkage to the actin cytoskeleton mediated by catenins. We transfected alpha-catenin-deficient colon carcinoma cells with a series of alpha-catenin constructs to determine that alpha-catenin expression increases the resistance to apoptosis induced by sphingosine. Two groups of constructs, containing deletions in either the middle segment of the molecule or the COOH terminus, induced morphological changes, cell compaction, and decreases in cell death. In alpha-catenin-expressing cells, ***inhibition*** of cadherin cell adhesion by treatment with anti- ***E*** - ***cadherin*** antibodies did not decrease the cells viability. alpha-Catenin expression partially suppressed the downregulation of Bcl-xL and the activation of caspase 3. Expression of p27kip1 protein, an ***inhibitor*** of cyclin-dependent kinases, was increased by alpha-catenin expression in low density cell cultures. The increased levels of p27kip1 correlated with both increased resistance to cell death and morphological changes in transfectants containing deletion ***mutants*** . Transfection-mediated upregulation of p27kip1 decreases sphingosine-induced cell death in alpha-catenin-deficient cells. We postulate that alpha-catenin mediates transduction of signals from the cadherin-catenin complex to regulate the apoptotic cascade via p27kip1.

L16 ANSWER 12 OF 32 MEDLINE
ACCESSION NUMBER: 2001349679 MEDLINE
DOCUMENT NUMBER: 21305937 PubMed ID: 11412025
TITLE: Activated armadillo/beta-catenin does not play a general

role in cell migration and process extension in Drosophila.
AUTHOR: Loureiro J J; [redacted]ng K; Cayirlioglu P; Baltus A [redacted]DiAntonio A; Peifer M
CORPORATE SOURCE: Department of Biology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3280, USA.
CONTRACT NUMBER: GM47857 (NIGMS)
SOURCE: DEVELOPMENTAL BIOLOGY, (2001 Jul 1) 235 (1) 33-44.
Journal code: 0372762. ISSN: 0012-1606.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010806
Last Updated on STN: 20010806
Entered Medline: 20010802

AB Human ***beta*** - ***catenin*** and its fly homolog Armadillo are best known for their roles in cadherin-based cell-cell adhesion and in transduction of Wingless/Wnt signals. It has been hypothesized that ***beta*** - ***catenin*** may also regulate cell migration and cell shape changes, possibly by regulating the microtubule cytoskeleton via ***interactions*** with ***APC*** . This hypothesis was based on experiments in which a hyperstable ***mutant*** form of ***beta*** - ***catenin*** was expressed in MDCK cells, where it altered their migratory properties and their ability to send out long cellular processes. We tested the generality of this hypothesis in vivo in Drosophila. We utilized three model systems in which cell migration and/or process extension are known to play key roles during development: the migration of the border cells during oogenesis, the extension of axons in the nervous system, and the migration and cell process extension of tracheal cells. In all cases, cells expressing activated Armadillo were able to migrate and extend cell processes essentially normally. The one alteration from normal involved an apparent cell fate change in certain tracheal cells. These results suggest that only certain cells are ***affected*** by activation of Armadillo/ ***beta*** - ***catenin*** , and that Armadillo/ ***beta*** - ***catenin*** does not play a general role in ***inhibiting*** cell migration or process extension.

L16 ANSWER 13 OF 32 MEDLINE
ACCESSION NUMBER: 2001184232 MEDLINE
DOCUMENT NUMBER: 21139110 PubMed ID: 11245482
TITLE: Geldanamycin abrogates ErbB2 association with proteasome-resistant beta-catenin in melanoma cells, increases beta-catenin-E-cadherin association, and decreases beta-catenin-sensitive transcription.
AUTHOR: Bonvini P; An W G; Rosolen A; Nguyen P; Trepel J; Garcia de Herreros A; Dunach M; Neckers L M
CORPORATE SOURCE: Department of Cell and Cancer Biology, Medicine Branch, National Cancer Institute, Rockville, Maryland 20850, USA.
SOURCE: CANCER RESEARCH, (2001 Feb 15) 61 (4) 1671-7.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB ***Beta*** - ***catenin*** undergoes both serine and tyrosine phosphorylation. Serine phosphorylation in the amino terminus targets ***beta*** - ***catenin*** for proteasome degradation, whereas tyrosine phosphorylation in the COOH terminus influences ***interaction*** with ***E*** - ***cadherin*** . We examined the tyrosine phosphorylation status of ***beta*** - ***catenin*** in melanoma cells expressing proteasome-resistant ***beta*** - ***catenin*** , as well as the effects that perturbation of ***beta*** - ***catenin*** tyrosine phosphorylation had on its association with ***E*** - ***cadherin*** and on its transcriptional activity. ***Beta*** - ***catenin*** is tyrosine phosphorylated in three melanoma cell lines and associates with both the ErbB2 receptor tyrosine

kinase and the LAR receptor tyrosine phosphatase. Geldanamycin, a drug which destabilizes ErbB2, caused rapid cellular depletion of the kinase and loss of its association with ***beta*** - ***catenin*** without perturbing either LAR or ***beta*** - ***catenin*** levels or LAR/ ***beta*** - ***catenin*** association. Geldanamycin also stimulated tyrosine dephosphorylation of ***beta*** - ***catenin*** and increased ***beta*** - ***catenin*** / ***E*** - ***cadherin*** association, resulting in substantially decreased cell motility. Geldanamycin also decreased the nuclear ***beta*** - ***catenin*** level and ***inhibited*** ***beta*** - ***catenin*** -driven transcription, as assessed using two different ***beta*** - ***catenin*** -sensitive reporters and the endogenous cyclin D1 gene. These findings were confirmed by transient transfection of two ***beta*** - ***catenin*** point ***mutants*** , Tyr-654Phe and Tyr-654Glu, which, respectively, mimic the dephosphorylated and phosphorylated states of Tyr-654, a tyrosine residue contained within the ***beta*** - ***catenin*** -ErbB2-binding domain. These data demonstrate that the functional activity of proteasome-resistant ***beta*** - ***catenin*** is regulated further by geldanamycin-sensitive tyrosine phosphorylation in melanoma cells.

L16 ANSWER 14 OF 32 MEDLINE
ACCESSION NUMBER: 2001164254 MEDLINE
DOCUMENT NUMBER: 21155779 PubMed ID: 11265645
TITLE: Wnt signaling is required for thymocyte development and activates Tcf-1 mediated transcription.
AUTHOR: Staal F J; Meeldijk J; Moerer P; Jay P; van de Weerdt B C; Vainio S; Nolan G P; Clevers H
CORPORATE SOURCE: Department of Immunology and Center for Biomedical Genetics, Utrecht Medical Center, Utrecht, The Netherlands.
SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (2001 Jan) 31 (1) 285-93. Journal code: 1273201. ISSN: 0014-2980.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329
AB T cell factor / lymphocyte enhancer factor (Tcf/Lef) ***transcription*** ***factors*** complex with the transcriptional co-activator ***beta*** - ***catenin*** to transduce Wnt signals in a variety of developmental systems. The prototypic family member Tcf-1 is highly expressed in T lineage cells. Tcf1-/- mice are defective in cell cycling of early thymocyte stages. Here, we show that the ***interaction*** of ***beta*** - ***catenin*** with Tcf-1 is required for full thymocyte development. This ***interaction*** may be established by signals mediated by Wnt1 and Wnt4, leading to increased Tcf-dependent transcriptional activity in thymocytes, as demonstrated in Tcf-LacZ reporter mice. Transduction of fetal thymocytes with Wnt1 and Wnt4 results in increased survival in an in vitro cell culture system. Retroviral expression of soluble Wnt receptor ***mutants*** that block Wnt signaling ***inhibits*** thymocyte development. These results imply an important role for the Wnt cascade in thymocyte development.

L16 ANSWER 15 OF 32 MEDLINE
ACCESSION NUMBER: 2001124292 MEDLINE
DOCUMENT NUMBER: 21028108 PubMed ID: 11156412
TITLE: Truncation of the extracellular region abrogrates cell contact but retains the growth-suppressive activity of E-cadherin.
AUTHOR: Sasaki C Y; Lin H; Morin P J; Longo D L
CORPORATE SOURCE: Laboratories of Immunology, National Institute on Aging, NIH, Baltimore, Maryland 21224, USA.
SOURCE: CANCER RESEARCH, (2000 Dec 15) 60 (24) 7057-65. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200102

ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010222

AB ***E*** - ***cadherin*** has been demonstrated to induce growth suppression and decrease the invasiveness of cancer cells and thus has been proposed to be a tumor suppressor gene. The ability of ***E*** - ***cadherin*** to mediate cell-cell contact and contact ***inhibition*** presumably accounts for its antitumor effects, which are attributed to the extracellular domain of the protein. Here we report that blocking the ability of ***E*** - ***cadherin*** to mediate contact ***inhibition*** by either antagonistic antibodies or expression of a ***mutant*** form of ***E*** - ***cadherin*** with the extracellular region deleted does not abrogate growth suppression. Transfection of the ***E*** - ***cadherin*** gene into the human prostate cancer cell line TSU.Pr-1 induced cell-cell contact formation, growth suppression, and redistribution of ***beta*** - ***catenin*** to the cell membrane. Treatment of the ***E*** - ***cadherin*** transfectant (CAD) with blocking antibodies disrupted cell-cell contact formation but did not influence the growth rate, suggesting that cell-cell ***interaction*** is not required for ***E*** - ***cadherin*** -mediated growth suppression. Similarly, transfection of an ***E*** - ***cadherin*** construct in which the NH2-terminal (extracellular) region was deleted did not allow cell-cell contact formation but induced growth suppression. In contrast, transfection of an ***E*** - ***cadherin*** construct in which the COOH-terminal (cytoplasmic) region was deleted did not induce suppression but promoted cell contact formation. In cells expressing ***E*** - ***cadherin*** lacking the cytoplasmic region, ***beta*** - ***catenin*** was evenly distributed in the cytoplasm. By contrast, in cells expressing ***E*** - ***cadherin*** lacking the extracellular region, ***beta*** - ***catenin*** was cell membrane associated. Growth suppression was always associated with the localization of ***beta*** - ***catenin*** to the cell membrane. The redistribution of ***beta*** - ***catenin*** from the cytoplasm to the cell membrane initially suggested the involvement of the Wnt signaling pathway in regulating cell growth. However, only small differences in ***beta*** - ***catenin*** /T-cell factor signaling were detected in control and ***E*** - ***cadherin*** -expressing cells, suggesting that the Wnt pathway is not involved. Taken together, these findings suggest that ***E*** - ***cadherin*** -induced growth ***inhibition*** may not be solely attributed to contact ***inhibition*** but may involve the redistribution of ***beta*** - ***catenin*** from the cytoplasm to the cell membrane, and this redistribution may ***affect*** growth pathways independent of T-cell factor.

L16 ANSWER 16 OF 32 MEDLINE
ACCESSION NUMBER: 2001013612 MEDLINE
DOCUMENT NUMBER: 20464902 PubMed ID: 11007949
TITLE: Integrin-linked kinase (ILK): a "hot" therapeutic target.
AUTHOR: Yoganathan T N; Costello P; Chen X; Jabali M; Yan J; Leung D; Zhang Z; Yee A; Dedhar S; Sanghera J
CORPORATE SOURCE: Kinetek Pharmaceuticals Inc., Vancouver, BC V6P6P2, Canada.. nathan@kinetekpharm.com
SOURCE: BIOCHEMICAL PHARMACOLOGY, (2000 Oct 15) 60 (8) 1115-9. Ref: 26
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200010
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20020420
Entered Medline: 20001031

AB Integrin-mediated cell adhesion is known to regulate gene expression through the activation of ***transcription*** ***factors*** . We have recently revealed that these activations are mediated through integrin-linked kinase (ILK). ILK is an ankyrin repeat-containing serine-threonine protein kinase that can ***interact*** directly with the cytoplasmic domain of the beta1 and beta3 integrin subunits and whose

kinase activity is modulated by cell-extracellular matrix ***interactions*** . We have shown that ILK overexpression results in the translocation of ***beta*** - ***catenin*** to the nucleus, which then forms a complex formation with the lymphoid enhancer binding factor 1 (***LEF*** - ***1***) ***transcription*** ***factor*** , subsequently activating the transcriptional activity of promoters containing ***LEF*** - ***1*** response elements. ILK phosphorylates the glycogen synthase kinase-3 (GSK-3), which ***inhibits*** GSK-3 activity. We have demonstrated that ILK stimulates activator protein-1 transcriptional activity through GSK-3 and the subsequent regulation of the c-Jun-DNA ***interaction*** . ILK also phosphorylates protein kinase B (PKB/Akt) and stimulates its activity. We have shown that ILK is an upstream effector of the phosphatidylinositol 3-kinase-dependent regulation of PKB/Akt. ILK has been shown to phosphorylate PKB/Akt on Ser-473 in vitro and in vivo. Our results clearly indicate that ILK is a key element in the regulation of integrin signaling as well as growth factor and Wnt signaling pathways. PTEN (phosphatase and tensin homolog detected on chromosome 10) is a tumor suppressor gene located on chromosome 10q23 that encodes a protein and phospholipid phosphatase. It is now estimated that inactivation ***mutants*** of PTEN exist in 60% of all forms of solid tumors. Loss of expression or mutational inactivation of PTEN leads to the constitutive activation of PKB/Akt via enhanced phosphorylation of Thr-308 and Ser-473. We have demonstrated that the activity of ILK is constitutively elevated in PTEN ***mutant*** cells. A small molecule ILK ***inhibitor*** suppresses the phosphorylation of PKB at the Ser-473 but not the Thr-308 site in the PTEN ***mutant*** cells. These results indicate that ***inhibition*** of ILK may be of significant value in solid tumor therapy.

L16 ANSWER 17 OF 32 MEDLINE
ACCESSION NUMBER: 2000268264 MEDLINE
DOCUMENT NUMBER: 20268264 PubMed ID: 10807598
TITLE: Selective degradation of E-cadherin and dissolution of E-cadherin-catenin complexes in epithelial ischemia.
AUTHOR: Bush K T; Tsukamoto T; Nigam S K
CORPORATE SOURCE: Department of Medicine, University of California, San Diego, La Jolla, CA 92093-0693, USA.
CONTRACT NUMBER: RO1
SOURCE: AMERICAN JOURNAL OF PHYSIOLOGY. RENAL PHYSIOLOGY, (2000 May) 278 (5) F847-52.
Journal code: 100901990. ISSN: 0363-6127.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000622
Last Updated on STN: 20000622
Entered Medline: 20000612

AB Ischemic epithelial cells are characterized by disruption of intercellular junctions and loss of apical-basolateral protein polarity, which are normally dependent on the integrity of the adherens junction (AJ). Biochemical analysis of both whole ischemic kidneys and ATP-depleted Madin-Darby canine kidney (MDCK) cells demonstrated a striking loss of ***E*** - ***cadherin*** (the transmembrane protein of the AJ) with the appearance and accumulation of an approximately 80-kDa ***fragment*** reactive with anti- ***E*** - ***cadherin*** antibodies on Western blots of ATP-depleted MDCK cells. This apparent ischemia-induced degradation of ***E*** - ***cadherin*** was not blocked by either ***inhibitors*** of the major proteolytic pathways (i.e., proteasome, lysosome, or calpain), or by chelation of intracellular calcium, suggesting the involvement of a protease capable of functioning at low ATP and low calcium levels. Immunocytochemistry revealed the movement of several proteins normally comprising the AJ, including ***E*** - ***cadherin*** and ***beta*** - ***catenin*** , away from lateral portions of the plasma membrane to intracellular sites. Moreover, rate-zonal centrifugation and immunoprecipitation with anti- ***E*** - ***cadherin*** and anti- ***beta*** - ***catenin*** antibodies indicated that ATP depletion disrupted normal ***E*** - ***cadherin*** -catenin ***interactions*** , resulting in the dissociation of alpha- and gamma-catenin from ***E*** - ***cadherin*** and ***beta*** - ***catenin*** -containing complexes. Because the

generation and maintenance of [redacted]larized epithelial cells are dependent upon ***E*** - ***cadheri[redacted]*** -mediated cell-cell adhesio[redacted]nd normal AJ function, we propose that the rapid degradation of ***E*** - ***cadherin*** and dissolution of the AJ is a key step in the development of the ischemic epithelial cell phenotype. Furthermore, we hypothesize that the reassembly of the AJ after ischemia/ATP depletion may require a novel bioassembly mechanism involving recombination of newly synthesized and sorted ***E*** - ***cadherin*** with preexisting pools of catenins that have (temporally) redistributed intracellularly.

L16 ANSWER 18 OF 32 MEDLINE
ACCESSION NUMBER: 2000260596 MEDLINE
DOCUMENT NUMBER: 20260596 PubMed ID: 10803460
TITLE: Differential interaction of plakoglobin and beta-catenin with the ubiquitin-proteasome system.
AUTHOR: Sadot E; Simcha I; Iwai K; Ciechanover A; Geiger B; Ben-Ze'ev A
CORPORATE SOURCE: Department of Molecular Cell Biology, The Weizmann Institute of Science, Rehovot, Israel.
SOURCE: ONCOGENE, (2000 Apr 13) 19 (16) 1992-2001. Journal code: 8711562. ISSN: 0950-9232.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000606
Last Updated on STN: 20000606
Entered Medline: 20000525
AB ***Beta*** - ***catenin*** and plakoglobin are closely related armadillo family proteins with shared and distinct properties; Both are associated with cadherins in actin-containing adherens junctions. Plakoglobin is also found in desmosomes where it anchors intermediate filaments to the desmosomal plaques. ***Beta*** - ***catenin*** , on the other hand, is a component of the Wnt signaling pathway, which is involved in embryonic morphogenesis and tumorigenesis. A key step in the regulation of this pathway involves modulation of ***beta*** - ***catenin*** stability. A multiprotein complex, regulated by Wnt, directs the phosphorylation of ***beta*** - ***catenin*** and its degradation by the ubiquitin-proteasome system. Plakoglobin can also associate with members of this complex, but ***inhibition*** of proteasomal degradation has little effect on its levels while dramatically increasing the levels of ***beta*** - ***catenin*** . Beta-TrCP, an F-box protein of the SCF E3 ubiquitin ligase complex, was recently shown to play a role in the turnover of ***beta*** - ***catenin*** . To elucidate the basis for the apparent differences in the turnover of ***beta*** - ***catenin*** and plakoglobin we compared the handling of these two proteins by the ubiquitin-proteasome system. We show here that a deletion ***mutant*** of beta-TrCP, lacking the F-box, can stabilize the endogenous ***beta*** - ***catenin*** leading to its nuclear translocation and induction of ***beta*** - ***catenin*** / ***LEF*** - ***1*** -directed transcription, without ***affecting*** the levels of plakoglobin. However, when plakoglobin was overexpressed, it readily associated with beta-TrCP, efficiently competed with ***beta*** - ***catenin*** for binding to beta-TrCP and became polyubiquitinated. Fractionation studies revealed that about 85% of plakoglobin in 293 cells, is Triton X-100-insoluble compared to 50% of ***beta*** - ***catenin*** . These results suggest that while both plakoglobin and ***beta*** - ***catenin*** can comparably ***interact*** with beta-TrCP and the ubiquitination system, the sequestration of plakoglobin by the membrane-cytoskeleton system renders it inaccessible to the proteolytic machinery and stabilizes it.

L16 ANSWER 19 OF 32 MEDLINE
ACCESSION NUMBER: 2000233859 MEDLINE
DOCUMENT NUMBER: 20233859 PubMed ID: 10769211
TITLE: Different effects of dominant negative mutants of desmocollin and desmoglein on the cell-cell adhesion of keratinocytes.
AUTHOR: Hanakawa Y; Amagai M; Shirakata Y; Sayama K; Hashimoto K
CORPORATE SOURCE: Department of Dermatology, School of Medicine, Ehime University, Ehime, Japan.. hanakawa@m.ehime-u.ac.jp

SOURCE: JOURNAL OF CELL SCIENCE, (2000 May) 113 (Pt 10) 1803-11.
Journal code: [redacted]2457. ISSN: 0021-9533.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200008
ENTRY DATE: Entered STN: 20000811
Last Updated on STN: 20000811
Entered Medline: 20000801

AB Desmosomes contain two types of cadherin: desmocollin (Dsc) and desmoglein (Dsg). In this study, we examined the different roles that Dsc and Dsg play in the formation of desmosomes, by using dominant-negative ***mutants*** . We constructed recombinant adenoviruses (Ad) containing truncated ***mutants*** of ***E*** - ***cadherin*** , desmocollin 3a, and desmoglein 3 lacking a large part of their extracellular domains (EcaddeltaEC, Dsc3adeltaEC, Dsg3deltaEC), using the Cre-loxP Ad system to circumvent the problem of the toxicity of the ***mutants*** to virus-producing cells. When Dsc3adeltaEC Ad-infected HaCaT cells were cultured with high levels of calcium, ***E*** - ***cadherin*** and ***beta*** - ***catenin*** , which are marker molecules for the adherens junction, disappeared from the cell-cell contact sites, and cell-cell adhesion was disrupted. This also occurred in the cells infected with EcaddeltaEC Ad. With Dsg3deltaEC Ad infection, keratin insertion at the cell-cell contact sites was ***inhibited*** and desmoplakin, a marker of desmosomes, was stained in perinuclear dots while the adherens junctions remained intact. Dsc3adeltaEC Ad ***inhibited*** the induction of adherens junctions and the subsequent formation of desmosomes with the calcium shift, while Dsg3deltaEC Ad only ***inhibited*** the formation of desmosomes. To further determine whether Dsc3adeltaEC directly ***affected*** adherens junctions, mouse fibroblast L cells transfected with ***E*** - ***cadherin*** (LEC5) were infected with these ***mutant*** Ads. Both Dsc3adeltaEC and EcaddeltaEC ***inhibited*** the cell-cell adhesion of LEC5 cells, as determined by the cell aggregation assay, while Dsg3deltaEC did not. These results indicate that the dominant negative effects of Dsg3deltaEC were restricted to desmosomes, while those of Dsc3adeltaEC were observed in both desmosomes and adherens junctions. Furthermore, the cytoplasmic domain of Dsc3adeltaEC coprecipitated both plakoglobin and ***beta*** - ***catenin*** in HaCaT cells. In addition, ***beta*** - ***catenin*** was found to bind the endogenous Dsc in HaCaT cells. These findings lead us to speculate that Dsc ***interacts*** with components of the adherens junctions through ***beta*** - ***catenin*** , and plays a role in nucleating desmosomes after the adherens junctions have been established.

L16 ANSWER 20 OF 32 MEDLINE
ACCESSION NUMBER: 2000187544 MEDLINE
DOCUMENT NUMBER: 20187544 PubMed ID: 10722668
TITLE: Down-regulation of beta-catenin by the colorectal tumor suppressor APC requires association with Axin and beta-catenin.
AUTHOR: Kawahara K; Morishita T; Nakamura T; Hamada F; Toyoshima K; Akiyama T
CORPORATE SOURCE: Laboratory of Molecular and Genetic Information, Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113, Japan.
SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Mar 24) 275 (12) 8369-74.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000505
Last Updated on STN: 20000505
Entered Medline: 20000427

AB The tumor suppressor adenomatous polyposis coli (***APC***) is mutated in familial adenomatous polyposis and in sporadic colorectal tumors. ***APC*** forms a complex with ***beta*** - ***catenin*** , Axin, and glycogen synthase kinase-3beta and induces the degradation of

beta - ***catenin*** . In the present study, we examined whether ***APC*** association with Axin is required for degradation of ***beta*** - ***catenin*** . We found that a ***fragment*** of ***APC*** that induces ***beta*** - ***catenin*** degradation was rendered inactive by disruption of its Axin-binding sites. Also, overexpression of an Axin ***fragment*** spanning the regulator of the G-protein signaling domain ***inhibited*** ***APC*** -mediated ***beta*** - ***catenin*** degradation. An ***APC*** ***fragment*** with mutated ***beta*** - ***catenin*** -binding sites but intact Axin-binding sites also failed to induce degradation of ***beta*** - ***catenin*** . These results suggest that ***APC*** requires ***interaction*** with Axin and ***beta*** - ***catenin*** to down-regulate ***beta*** - ***catenin*** .

L16 ANSWER 21 OF 32 MEDLINE
ACCESSION NUMBER: 2000096725 MEDLINE
DOCUMENT NUMBER: 20096725 PubMed ID: 10629228
TITLE: Selective uncoupling of p120(ctn) from E-cadherin disrupts strong adhesion.
AUTHOR: Thoreson M A; Anastasiadis P Z; Daniel J M; Ireton R C; Wheelock M J; Johnson K R; Hummingbird D K; Reynolds A B
CORPORATE SOURCE: Department of Cell Biology, Vanderbilt University School of Medicine, Nashville, Tennessee 37232-2175, USA.
CONTRACT NUMBER: CA55724 (NCI)
CA69485 (NCI)
SOURCE: JOURNAL OF CELL BIOLOGY, (2000 Jan 10) 148 (1) 189-202.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200003
ENTRY DATE: Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000309
AB p120(ctn) is a catenin whose direct binding to the juxtamembrane domain of classical cadherins suggests a role in regulating cell-cell adhesion. The juxtamembrane domain has been implicated in a variety of roles including cadherin clustering, cell motility, and neuronal outgrowth, raising the possibility that p120 mediates these activities. We have generated minimal mutations in this region that uncouple the ***E*** - ***cadherin*** -p120 ***interaction*** , but do not ***affect*** ***interactions*** with other catenins. By stable transfection into ***E*** - ***cadherin*** -deficient cell lines, we show that cadherins are both necessary and sufficient for recruitment of p120 to junctions. Detergent-free subcellular fractionation studies indicated that, in contrast to previous reports, the stoichiometry of the ***interaction*** is extremely high. Unlike alpha- and ***beta*** - ***catenins*** , p120 was metabolically stable in cadherin-deficient cells, and was present at high levels in the cytoplasm. Analysis of cells expressing ***E*** - ***cadherin*** ***mutant*** constructs indicated that p120 is required for the ***E*** - ***cadherin*** -mediated transition from weak to strong adhesion. In aggregation assays, cells expressing p120-uncoupled ***E*** - ***cadherin*** formed only weak cell aggregates, which immediately dispersed into single cells upon pipetting. As an apparent consequence, the actin cytoskeleton failed to insert properly into peripheral ***E*** - ***cadherin*** plaques, resulting in the inability to form a continuous circumferential ring around cell colonies. Our data suggest that p120 directly or indirectly regulates the ***E*** - ***cadherin*** -mediated transition to tight cell-cell adhesion, possibly blocking subsequent events necessary for reorganization of the actin cytoskeleton and compaction.

L16 ANSWER 22 OF 32 MEDLINE
ACCESSION NUMBER: 1999215555 MEDLINE
DOCUMENT NUMBER: 99215555 PubMed ID: 10201372
TITLE: Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells.
AUTHOR: Tetsu O; McCormick F
CORPORATE SOURCE: University of California, San Francisco, School of Medicine, Cancer Research Institute, 94143-0128, USA.
SOURCE: NATURE, (1999 Apr 1) 398 (6726) 422-6.

Journal code: [illegible]0462. ISSN: 0028-0836.
PUB. COUNTRY: ENGLAND: Unite[illegible]ingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990511
Last Updated on STN: 20000303
Entered Medline: 19990429

AB Mutations in the adenomatous polyposis coli (***APC***) tumour-suppressor gene occur in most human colon cancers. Loss of functional ***APC*** protein results in the accumulation of ***beta*** - ***catenin*** . ***Mutant*** forms of ***beta*** - ***catenin*** have been discovered in colon cancers that retain wild-type ***APC*** genes, and also in melanomas, medulloblastomas, prostate cancer and gastric and hepatocellular carcinomas. The accumulation of ***beta*** - ***catenin*** activates genes that are responsive to ***transcription*** ***factors*** of the TCF/LEF family, with which ***beta*** - ***catenin*** ***interacts*** . Here we show that ***beta*** - ***catenin*** activates transcription from the cyclin D1 promoter, and that sequences within the promoter that are related to consensus TCF/LEF-binding sites are necessary for activation. The oncoprotein p21ras further activates transcription of the cyclin D1 gene, through sites within the promoter that bind the transcriptional regulators Ets or CREB. Cells expressing ***mutant*** ***beta*** - ***catenin*** produce high levels of cyclin D1 messenger RNA and protein constitutively. Furthermore, expression of a dominant-negative form of TCF in colon-cancer cells strongly ***inhibits*** expression of cyclin D1 without ***affecting*** expression of cyclin D2, cyclin E, or cyclin-dependent kinases 2, 4 or 6. This dominant-negative TCF causes cells to arrest in the G1 phase of the cell cycle; this phenotype can be rescued by expression of cyclin D1 under the cytomegalovirus promoter. Abnormal levels of ***beta*** - ***catenin*** may therefore contribute to neoplastic transformation by causing accumulation of cyclin D1.

L16 ANSWER 23 OF 32 MEDLINE
ACCESSION NUMBER: 1999175480 MEDLINE
DOCUMENT NUMBER: 99175480 PubMed ID: 10074433
TITLE: The F-box protein beta-TrCP associates with phosphorylated beta-catenin and regulates its activity in the cell.
AUTHOR: Hart M; Concordet J P; Lassot I; Albert I; del los Santos R; Durand H; Perret C; Rubinfeld B; Margottin F; Benarous R; Polakis P
CORPORATE SOURCE: Onyx Pharmaceuticals 3031 Research Drive Richmond California 94806 USA.
SOURCE: CURRENT BIOLOGY, (1999 Feb 25) 9 (4) 207-10.
Journal code: 9107782. ISSN: 0960-9822.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 19990504
Last Updated on STN: 20000303
Entered Medline: 19990422

AB Defects in ***beta*** - ***catenin*** regulation contribute to the neoplastic transformation of mammalian cells. Dysregulation of ***beta*** - ***catenin*** can result from missense mutations that ***affect*** critical sites of phosphorylation by glycogen synthase kinase 3beta (GSK3beta). Given that phosphorylation can regulate targeted degradation of ***beta*** - ***catenin*** by the proteasome, ***beta*** - ***catenin*** might ***interact*** with an E3 ubiquitin ligase complex containing an F-box protein, as is the case for certain cell cycle regulators. Accordingly, disruption of the Drosophila F-box protein Slimb upregulates the ***beta*** - ***catenin*** homolog Armadillo. We reasoned that the human homologs of Slimb - beta-TrCP and its isoform beta-TrCP2 (KIAA0696) - might ***interact*** with ***beta*** - ***catenin*** . We found that the binding of beta-TrCP to ***beta*** - ***catenin*** was direct and dependent upon the WD40 repeat sequences in beta-TrCP and on phosphorylation of the GSK3beta sites in ***beta*** - ***catenin*** . Endogenous

beta - ***catenin*** and beta-TrCP could be coimmunoprecipitated from mammalian cells. Overexpression of wild-type beta-TrCP in mammalian cells promoted the downregulation of ***beta*** - ***catenin*** , whereas overexpression of a dominant-negative deletion ***mutant*** upregulated ***beta*** - ***catenin*** protein levels and activated signaling dependent on the ***transcription*** ***factor*** Tcf. In contrast, beta-TrCP2 did not associate with ***beta*** - ***catenin*** . We conclude that beta-TrCP is a component of an E3 ubiquitin ligase that is responsible for the targeted degradation of phosphorylated ***beta*** - ***catenin*** .

L16 ANSWER 24 OF 32 MEDLINE
ACCESSION NUMBER: 1999156980 MEDLINE
DOCUMENT NUMBER: 99156980 PubMed ID: 10037790
TITLE: Coupling assembly of the E-cadherin/beta-catenin complex to efficient endoplasmic reticulum exit and basal-lateral membrane targeting of E-cadherin in polarized MDCK cells.
AUTHOR: Chen Y T; Stewart D B; Nelson W J
CORPORATE SOURCE: Department of Molecular and Cellular Physiology, Stanford University School of Medicine, Stanford, California 94305-5435, USA.
SOURCE: JOURNAL OF CELL BIOLOGY, (1999 Feb 22) 144 (4) 687-99. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 19990628
Last Updated on STN: 19990628
Entered Medline: 19990614
AB The ***E*** - ***cadherin*** /catenin complex regulates Ca++-dependent cell-cell adhesion and is localized to the basal-lateral membrane of polarized epithelial cells. Little is known about mechanisms of complex assembly or intracellular trafficking, or how these processes might ultimately regulate adhesion functions of the complex at the cell surface. The cytoplasmic domain of ***E*** - ***cadherin*** contains two putative basal-lateral sorting motifs, which are homologous to sorting signals in the low density lipoprotein receptor, but an alanine scan across tyrosine residues in these motifs did not ***affect*** the fidelity of newly synthesized ***E*** - ***cadherin*** delivery to the basal-lateral membrane of MDCK cells. Nevertheless, sorting signals are located in the cytoplasmic domain since a chimeric protein (GP2CAD1), comprising the extracellular domain of GP2 (an apical membrane protein) and the transmembrane and cytoplasmic domains of ***E*** - ***cadherin*** , was efficiently and specifically delivered to the basal-lateral membrane. Systematic deletion and recombination of specific regions of the cytoplasmic domain of GP2CAD1 resulted in delivery of <10% of these newly synthesized proteins to both apical and basal-lateral membrane domains. Significantly, >90% of each ***mutant*** protein was retained in the ER. None of these ***mutants*** formed a strong ***interaction*** with ***beta*** - ***catenin*** , which normally occurs shortly after ***E*** - ***cadherin*** synthesis. In addition, a simple deletion mutation of ***E*** - ***cadherin*** that lacks ***beta*** - ***catenin*** binding is also localized intracellularly. Thus, ***beta*** - ***catenin*** binding to the whole cytoplasmic domain of ***E*** - ***cadherin*** correlates with efficient and targeted delivery of ***E*** - ***cadherin*** to the lateral plasma membrane. In this capacity, we suggest that ***beta*** - ***catenin*** acts as a chauffeur, to facilitate transport of ***E*** - ***cadherin*** out of the ER and the plasma membrane.

L16 ANSWER 25 OF 32 MEDLINE
ACCESSION NUMBER: 1998374323 MEDLINE
DOCUMENT NUMBER: 98374323 PubMed ID: 9707618
TITLE: A novel frizzled gene identified in human esophageal carcinoma mediates APC/beta-catenin signals.
AUTHOR: Tanaka S; Akiyoshi T; Mori M; Wands J R; Sugimachi K
CORPORATE SOURCE: Department of Surgery, Medical Institute of Bioregulation, and Department of Surgery II, Faculty of Medicine, Kyushu University, Japan.. shinji@tsurumi.beppu.kyushu-u.ac.jp
CONTRACT NUMBER: CA-35711 (NCI)

SOURCE: PROCEEDINGS OF [redacted]E NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES [redacted]AMERICA, (1998 Aug 18) 95 (17) [redacted]164-9. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
OTHER SOURCE: GENBANK-AB010881
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980917

AB A novel member of the human frizzled (Fz) gene family was cloned and found to be specifically expressed in 3 of 13 well differentiated (23%), 13 of 20 moderately differentiated (62%), and 12 of 14 poorly differentiated (86%) squamous cell esophageal carcinomas compared with the adjacent uninvolved normal mucosa. The FzE3 cDNA encodes a protein of 574 amino acids and shares high sequence homology with the human FzD2 gene particularly in the putative ligand binding region of the cysteine-rich extracellular domain. Functional analysis revealed that transfection and expression of the FzE3 cDNA in esophageal carcinoma cells stimulates complex formation between adenomatous polyposis coli (***APC***) and ***beta*** - ***catenin*** followed by nuclear translocation of ***beta*** - ***catenin*** . Furthermore, cotransfection of a ***mutant*** construct encoding a FzE3 protein with a C-terminal truncation completely ***inhibited*** the ***interaction*** of ***APC*** with ***beta*** - ***catenin*** in cells. Finally, coexpression of FzE3 with ***Lef*** - ***1*** ***transcription*** ***factor*** enhanced ***beta*** - ***catenin*** translocation to the nucleus. These observations suggest that FzE3 gene expression may down-regulate ***APC*** function and enhance ***beta*** - ***catenin*** mediated signals in poorly differentiated human esophageal carcinomas.

L16 ANSWER 26 OF 32 MEDLINE
ACCESSION NUMBER: 1998292519 MEDLINE
DOCUMENT NUMBER: 98292519 PubMed ID: 9628899
TITLE: Differential nuclear translocation and transactivation potential of beta-catenin and plakoglobin.
AUTHOR: Simcha I; Shtutman M; Salomon D; Zhurinsky J; Sadot E; Geiger B; Ben-Ze'ev A
CORPORATE SOURCE: Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot 76100, Israel.
SOURCE: JOURNAL OF CELL BIOLOGY, (1998 Jun 15) 141 (6) 1433-48. Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
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AB ***beta*** - ***Catenin*** and plakoglobin are homologous proteins that function in cell adhesion by linking cadherins to the cytoskeleton and in signaling by transactivation together with lymphoid-enhancing binding/T cell (LEF/TCF) ***transcription*** ***factors*** . Here we compared the nuclear translocation and transactivation abilities of ***beta*** - ***catenin*** and plakoglobin in mammalian cells. Overexpression of each of the two proteins in MDCK cells resulted in nuclear translocation and formation of nuclear aggregates. The ***beta*** - ***catenin*** -containing nuclear structures also contained ***LEF*** - ***1*** and vinculin, while plakoglobin was inefficient in recruiting these molecules, suggesting that its ***interaction*** with ***LEF*** - ***1*** and vinculin is significantly weaker. Moreover, transfection of ***LEF*** - ***1*** translocated endogenous ***beta*** - ***catenin*** , but not plakoglobin to the nucleus. Chimeras consisting of Gal4 DNA-binding domain and the transactivation domains of either plakoglobin or ***beta*** - ***catenin*** were equally potent in transactivating a Gal4-responsive reporter, whereas activation of ***LEF*** - ***1*** - responsive transcription was significantly higher with ***beta*** - ***catenin***

. Overexpression of wild-type plakoglobin or ***mutant*** ***beta*** - ***catenin*** lacking the transactivation domain induced accumulation of the endogenous ***beta*** - ***catenin*** in the nucleus and ***LEF*** - ***1*** -responsive transactivation. It is further shown that the constitutive ***beta*** - ***catenin*** -dependent transactivation in SW480 colon carcinoma cells and its nuclear localization can be ***inhibited*** by overexpressing N-cadherin or alpha-catenin. The results indicate that (a) plakoglobin and ***beta*** - ***catenin*** differ in their nuclear translocation and complexing with ***LEF*** - ***1*** and vinculin; (b) ***LEF*** - ***1*** -dependent transactivation is preferentially driven by ***beta*** - ***catenin*** ; and (c) the cytoplasmic partners of ***beta*** - ***catenin*** , cadherin and alpha-catenin, can sequester it to the cytoplasm and ***inhibit*** its transcriptional activity.

L16 ANSWER 27 OF 32 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:189197 CAPLUS
DOCUMENT NUMBER: 130:232471
TITLE: The protein conductin and its application for diagnosis and gene therapy of colon cancer
INVENTOR(S): Behrens, Jurgen; Birchmeier, Walter
PATENT ASSIGNEE(S): Max-Delbruck-Centrum fur Molekulare Medizin, Germany
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911780	A2	19990311	WO 1998-DE2621	19980901
WO 9911780	A3	19990527		
W: CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
DE 19840875	A1	19990512	DE 1998-19840875	19980901
EP 1029047	A2	20000823	EP 1998-954120	19980901
R: AT, BE, CH, DE, DK, FR, GB, IT, LI, NL, SE, FI				

PRIORITY APPLN. INFO.: DE 1997-19738205 A 19970902
WO 1998-DE2621 W 19980901

AB The invention concerns the novel protein ***conductin*** that is able to regulate the . ***beta*** .- ***catenin*** function and ***interacts*** with the tumor suppressor adenomatous polyposis coli (***APC***); and its application in the gene therapy of colon cancer. The 840 amino acid contg. protein contains domains with various activities: 78-200 is the RGS (Regulator of G-Protein Signalling) binding sequence; 343-396 is the GSK 3.beta. (glycogen synthase kinase 3.beta.) binding sequence; 397-465 is the . ***beta*** .- ***catenin*** binding sequence; 783-833 is the Dishevelled homol. region. Mutations, variants and ***fragments*** of ***conductin*** with the corresponding coding genes and mRNA sequences are also included. Antibodies and nucleic acid probes for the detection of ***conductin*** are part of the diagnosis tools. For therapeutic purposes a vector contg. the ***conductin*** gene is constructed; substances that activate and reactivate ***conductin*** in the body are co-administered, e.g. a substance that activates the ***conductin*** promoter or stabilizes mRNA. The effect of ***conductin*** was proved using SW480 cells with ***APC*** mutation and thus increased . ***beta*** .- ***catenin*** level. Introduction of ***conductin*** resulted in the decrease of . ***beta*** .- ***catenin*** to the same concn. as in non ***APC*** mutated SW480 cells. In an expt. with Xenopus embryos it was shown that ***conductin*** ***inhibits*** the Wnt/Wingless signaling pathway via its ***interaction*** with . ***beta*** .- ***catenin*** .

L16 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:578401 CAPLUS
DOCUMENT NUMBER: 129:328962
TITLE: Studies on colon tumorigenesis and therapy using Apc knockout mice
AUTHOR(S): Taketo, Makoto M.
CORPORATE SOURCE: Laboratory of Biomedical Genetics, Graduate School of

Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan
SOURCE: Yakubutsu Dotai (1998), 13(3), 273-279
CODEN: YADOEL; ISSN: 0916-1139
PUBLISHER: Nippon Yakubutsu Dotai Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, with 44 refs., discussing the mol. genetic studies of familial adenomatous polyposis (FAP) kindreds which led to the discovery of the ***APC*** (adenomatous polyposis coli) gene on human chromosome 5q21. Mutations in ***APC*** appear to be responsible for not only FAP but also many sporadic cancers of the colorectal axis, stomach, and esophagus. The ***APC*** protein contains regions that may form an .alpha.-helical coiled-coil structure, and a sub-domain of the first 55 aa form a stable, parallel helical dimer. Antibody studies showed that the wild-type, but not ***mutant*** , ***APC*** protein is assocd. with the microtubule cytoskeleton. The predicted structure of ***APC*** , its localization, and its ***interaction*** with . ***beta*** .- ***catenin*** suggested its involvement in cell adhesion. In fact, recent studies demonstrated that ***APC*** is localized to plasma membrane sites involved in active cell migration. At the same time, . ***beta*** .- ***catenin*** ***interacts*** with hTcf-4 and Lef ***transcription*** ***factors*** , hTct-4 transactivates transcription only when assocd. with . ***beta*** .- ***catenin*** . We recently constructed a gene knockout mouse strain in which the mouse homolog of the human ***APC*** was inactivated by homologous recombination. Using this mouse strain, we elucidated the mechanism how the polyp adenomas are formed in both morphol. and genetic aspects. At the same time, we investigated the effects of carcinogens and anticancer agents on the polypsis. Accumulating evidence indicates that nonsteroidal antiinflammatory drugs (NSAIDs) reduce the incidence of colorectal cancers in human and exptl. animals, and reduce the polyp no. and size in FAP patients. Recently, evidence has been presented that COX-2 is induced in human colorectal cancers, and in the polyps of mouse FAP models. Accordingly, we inactivated the COX-2 gene in our FAP model mice, and demonstrated that both the no. and size of polyps are reduced dramatically. In addn., a COX-2 selective ***inhibitor*** caused similar results to COX-2 gene knockout mutations. These genetic and pharmacol. data open the possibility of effectively treating human FAP and various cancers with COX-2 selective ***inhibitors*** , a new class of NSAIDs.

L16 ANSWER 29 OF 32 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2001:97123 BIOSIS
DOCUMENT NUMBER: PREV200100097123
TITLE: Function and molecular organization of the presenilin1/E-cadherin/catenin adherens junction system.
AUTHOR(S): Marambaud, P. (1); Baki, L.; Georgakopoulos, A.; Shioi, J.; Efthimiopoulos, S.; Ozawa, M.; Robakis, N. K.
CORPORATE SOURCE: (1) Mount Sinai School of Medicine, New York, NY USA
SOURCE: Society for Neuroscience Abstracts, (2000) Vol. 26, No. 1-2, pp. Abstract No.-298.13. print.
Meeting Info.: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000 Society for Neuroscience
. ISSN: 0190-5295.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Most cases of early onset familial Alzheimer's disease (FAD) are caused by mutations in presenilin 1 gene. We found that in epithelial cells, presenilin 1 (PS1) protein localizes at cell-cell contact sites and forms complexes with the cadherin-based adherens junctions. The cytoplasmic domain of cell surface cadherin regulates cell-cell adhesion by ***interacting*** with soluble protein factors, including beta- and gamma-catenin. We used ***E*** - ***cadherin*** deletion ***mutants*** which lack the beta-, and gamma-catenin binding sequence to show that the PS1/ ***E*** - ***cadherin*** ***interaction*** is independent of the catenin binding. Cross-linking experiments revealed that the cleaved carboxy-terminal ***fragment*** of PS1 binds directly to ***E*** - ***cadherin*** and an 11 amino acid sequence in the cytoplasmic domain of ***E*** - ***cadherin*** is necessary for this

interaction . Furhtermore, absence of PS1 destabilizes both the ***E*** - ***cadherin*** ***beta*** - ***catenin*** and ***E*** - ***cadherin*** /gamma-catenin complexes. Thus, our data shows that PS1 binds directly to the cytoplasmic domain of ***E*** - ***cadherin*** and stabilizes the cadherin/catenin cell-cell adhesion complex. Adherens junctions regulate cell-cell adhesion/communication and play important roles not only in organogenesis but also in tissue function of adult organisms. Incorporation of mutated PS1 in adherens junctions may ***affect*** function of many tissues including synaptic adhesion and permeability of the brain endothelium (supported by HIH grant AG08200, the Alzheimer Association and the Philippe Foundation).

L16 ANSWER 30 OF 32 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:103199 BIOSIS
DOCUMENT NUMBER: PREV200000103199
TITLE: Selective uncoupling of p120ctn from E-cadherin disrupts strong adhesion.
AUTHOR(S): Thoreson, Molly A.; Anastasiadis, Panos Z.; Daniel, Juliet M.; Ireton, Renee C.; Wheelock, Margaret J.; Johnson, Keith R.; Hummingbird, Diana K.; Reynolds, Albert B. (1)
CORPORATE SOURCE: (1) Department of Cell Biology, Vanderbilt University, MCN C-2310, Nashville, TN, 37232-2175 USA
SOURCE: Journal of Cell Biology, (Jan. 10, 1999) Vol. 148, No. 1, pp. 189-201.
ISSN: 0021-9525.
DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English
AB p120ctn is a catenin whose direct binding to the juxtamembrane domain of classical cadherins suggests a role in regulating cell-cell adhesion. The juxtamembrane domain has been implicated in a variety of roles including cadherin clustering, cell motility, and neuronal outgrowth, raising the possibility that p120 mediates these activities. We have generated minimal mutations in this region that uncouple the ***E*** - ***cadherin*** -p120 ***interaction*** , but do not ***affect*** ***interactions*** with other catenins. By stable transfection into ***E*** - ***cadherin*** -deficient cell lines, we show that cadherins are both necessary and sufficient for recruitment of p120 to junctions. Detergent-free subcellular fractionation studies indicated that, in contrast to previous reports, the stoichiometry of the ***interaction*** is extremely high. Unlike alpha- and ***beta*** - ***catenins*** , p120 was metabolically stable in cadherin-deficient cells, and was present at high levels in the cytoplasm. Analysis of cells expressing ***E*** - ***cadherin*** ***mutant*** constructs indicated that p120 is required for the ***E*** - ***cadherin*** -mediated transition from weak to strong adhesion. In aggregation assays, cells expressing p120-uncoupled ***E*** - ***cadherin*** formed only weak cell aggregates, which immediately dispersed into single cells upon pipetting. As an apparent consequence, the actin cytoskeleton failed to insert properly into peripheral ***E*** - ***cadherin*** plaques, resulting in the inability to form a continuous circumferential ring around cell colonies. Our data suggest that p120 directly or indirectly regulates the ***E*** - ***cadherin*** -mediated transition to tight cell-cell adhesion, possibly blocking subsequent events necessary for reorganization of the actin cytoskeleton and compaction.

L16 ANSWER 31 OF 32 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1994:205232 BIOSIS
DOCUMENT NUMBER: PREV199497218232
TITLE: Molecular organization and function of the cadherin-catenin complex.
AUTHOR(S): Ozawa, Masayuki
CORPORATE SOURCE: Dep. Biochem., Fac. Med., Kagoshima Univ., 8-35-1 Sakuragaoka, Kagoshima-city Japan
SOURCE: Membrane, (1994) Vol. 19, No. 1, pp. 23-32.
ISSN: 0385-1036.
DOCUMENT TYPE: Article
LANGUAGE: Japanese
SUMMARY LANGUAGE: English
AB ***E*** - ***cadherin*** (uvomorulin) is a member of the Ca-2+-dependent cell adhesion molecules (cadherins). Its cytoplasmic region complexes with structurally distinct proteins termed alpha-, beta-,

and gamma-catenins. cDNA clon[redacted] has revealed that alpha-catenin is a vinculin homologue whereas [redacted]beta*** - ***catenin*** is[redacted]osely related to plakoglobin. A specific recognition site for catenins has been located in a carboxyl-terminal 72 amino acid domain (the catenin-binding domain). The association with catenins is of crucial importance for the cell adhesion function of ***E*** - ***cadherin*** , since ***mutant*** ***E*** - ***cadherins*** with deletions in the catenin-binding domain show no activity in cell aggregation assays. A cell line, which express ***E*** - ***cadherin*** and catenins except for alpha-catenin, shows poor adhesiveness but transfection of cDNA for alpha-N-catenin, a subtype of alpha-catenin, results in an increased adhesiveness of the cells. A combination of biochemical analyses on the molecular organization of the ***E*** - ***cadherin*** -catenin complex has shown that a single complex is composed of one molecule of ***E*** - ***cadherin*** , one molecule of alpha-catenin, and one molecule of catenin. ***beta*** - ***catenin*** has been shown to ***interact*** directly with ***E*** - ***cadherin*** . In pulse-chase experiments ***beta*** - ***catenin*** is already associated with the 135 kD ***E*** - ***cadherin*** precursor molecule but the assembly of the newly synthesized alpha-, and gamma-catenin into the complex is only detected around the time of endoproteolytic processing. Transformation of cells with v-src results in tyrosine phosphorylation of the cadherin-catenin complex and perturbed cadherin-mediated cell adhesion whereas a tyrosine kinase ***inhibitor*** reverts the effect of transformation. These results suggest a possible role of the tyrosine phosphorylation of the complex in regulating cadherin function.

L16 ANSWER 32 OF 32 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2000159750 EMBASE
TITLE: Identification of a novel molecular target that regulates metastasis of human esophageal carcinoma.
AUTHOR: Tanaka S.; Sato K.; Mori M.; Sugimachi K.
CORPORATE SOURCE: S. Tanaka, Department of Surgery II, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Fukuoka 812-8582, Japan
SOURCE: Japanese Journal of Gastroenterological Surgery, (2000) 33/4 (529-532).
Refs: 6
ISSN: 0386-9768 CODEN: NSGZD5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: Japanese
SUMMARY LANGUAGE: English; Japanese
AB A novel member of the human frizzled (Fz) gene family was cloned and found to be specifically expressed compared to the adjacent uninvolved normal mucosa in 28 of 47 (60%) squamous cell esophageal carcinomas. The FzE3 cDNA encodes a protein of 574 amino acids and shares high sequence homology with other frizzled genes, particularly in the putative ligand-binding region of the cysteine-rich extracellular domain. Functional analysis revealed that transfection and expression of the FzE3 cDNA in esophageal carcinoma cells stimulates complex formation between ***APC*** and . ***beta*** .- ***catenin*** followed by nuclear translocation of . ***beta*** .- ***catenin*** , which mediates cell:cell attachment with ***E*** - ***cadherin*** . Furthermore, cotransfection of a ***mutant*** construct encoding a FzE3 protein with a C-terminal truncation completely ***inhibited*** the ***interaction*** of ***APC*** with . ***beta*** .- ***catenin*** in the cells. These observations suggest that FzE3 gene expression may downregulate ***APC*** function and enhance . ***beta*** .- ***catenin*** mediated signals in human esophageal carcinomas.

=> d his

(FILE 'HOME' ENTERED AT 14:12:17 ON 18 FEB 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT

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     14:12:44 ON 18 FEB 2003
L1         15203 S BETA CATENIN
L2        319392 S TRANSCRIPTION FACTOR
L3         12899 S (TUMOR SUPPRESSOR GENE PRODUCT) OR (TUMOR SUPPRESSOR PROTEIN)
L4         59642 S LEF-1 OR TCF-4 OR APC OR CONDUCTIN OR E-CADHERIN
L5        386028 S L2 OR L3 OR L4
L6          1839 S L1 (P) L5 (P) INTERACT?
L7           535 S L6 (P) INHIBIT?
L8           180 S L6 (P) AFFECT?
L9             0 S  L1 (P) (ARMADILLO ADJ DOMAIN)
L10           27 S (L7 OR L8) (P) PEPTIDE
L11            6 DUPLICATE REMOVE L10 (21 DUPLICATES REMOVED)
L12         1919 S L1 (P) (FRAGMENT OR MUTANT)
L13          334 S L12 (P) L5 (P) INTERACT?
L14          142 S L13 (P) (INHIBIT? OR AFFECT?)
L15           35 DUPLICATE REMOVE L14 (107 DUPLICATES REMOVED)
L16           32 S L15 NOT L11

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